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(54) Pharmaceutical compositions comprising co-micronized fenofibrate

(57) A pharmaceutical composition for oral administration comprising a co-micronized mixture of fenofibrate and a solid excipient that is not a surfactant.

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Description

FIELD OF INVENTION

[0001] The present invention relates to pharmaceutical compositions for oral administration comprising fenofibrate which enable improve dissolution and bioavailability.

BACKGROUND

[0002] Fenofibrate is practically insoluble in water. This causes fenofibrate to exhibit a low rate of dissolution in aqueous media (including gastrointestinal fluids). Which results in inadequate bioavailability (absorption into systemic circulation) after oral ingestion.

[0003] In order to make a composition comprising fenofibrate that will enable maximum bioavailability, it is necessary to incorporate into the composition a feature that increases the rate of dissolution of the drug in gastrointestinal fluids.

[0004] Several ways of increasing the rate of dissolution of drugs having low solubility in water are known in the prior art.

[0005] One approach is micronization. In this approach, the drug is milled to fine particles, typically having a mean diameter of under about 15 microns. A second approach is to include a surfactant in the composition.

[0006] For the drug fenofibrate, neither micronization alone nor use of a surfactant alone enables maximum bioavailability. US Patent 4895726 discloses that the rate of dissolution and the bioavailability of fenofibrate can be maximized by co-micronization of fenofibrate with a solid surfactant. In this process the fenofibrate is first mixed with the solid surfactant and then the mixture is micronized.

[0007] A composition made according to the invention of US Patent 4895726 is sold in Canada under the tradename Lipidil Micro and in the United States under the tradename Tricor.

A disadvantage of the technology of US Patent 4895726 is the need to include the solid surfactant in the composition. Because of the toxicity of surfactants, it is preferable to avoid use of a surfactant if possible.

Another method of increasing the dissolution rate of fenofibrate is disclosed in Canadian patent application No. 2214895. This publication discloses that the bioavailability of fenofibrate can be improved by making a solid dispersion of a disintegrant in the fenofibrate. This is done by melting the fenofibrate, blending the disintegrant into the molten fenofibrate, and resolidifying the mixture. The resulting solid can then be ground up into granules and the granules used to make the final composition. For example, the granules can be filled into two-piece hard gelatin capsules.

[0008] A disadvantage of the method of Canadian patent application No. 2214895 is that it requires the use of specialized equipment to make the molten blend.

[0009] In view of the limitations of the prior art, it is the object of the present invention to enable increased dissolution rate of fenofibrate without the need to incorporate a surfactant in the composition, and without the need to make a molten blend.

DESCRIPTION OF THE INVENTION

[0010] It has been found that the dissolution rate of fenofibrate can be substantially increased by co-micronization of fenofibrate with a pharmaceutically acceptable excipient that is not a surfactant. This is surprising in light of the US Patent 4895726 which teaches co-micronization only with a solid surfactant.

[0011] The term "pharmaceutically acceptable excipient" will be understood to mean any ingredient having no therapeutic activity and being nontoxic and thus suitable as an excipient.

[0012] Suitable excipients will include any of the excipients commonly used in pharmaceutical products, such as, for example, microcrystalline cellulose, lactose and starch, provided that such excipient is solid at room temperature and not a surfactant.

[0013] The ratio of the weight of the excipient to the weight to fenofibrate may be anywhere from about 1:100 to about 2:1, will preferably be from about 1:10 to about 3:2, and will most preferably be about 1:1.

[0014] The co-micronization of the fenofibrate and excipient will advantageously be carried out by mixing the fenofibrate and excipient together and then micronizing of the mixture on conventional micronization equipment, such as an air-jet mill. The mixture will preferably be micronized such that the mean particle size is less than 15 microns, more preferably less than 10 microns, and most preferably less than 5 microns.

[0015] The co-micronized powder may then be processed into solid dosage forms for oral administration (i.e. tablets or capsules).

[0016] This may be, for example, in one of the following ways:

1. Filling the co-micronized powder directly into 2-piece hard gelatin capsules.

2. Mixing the co-micronized powder with other excipients, such as, for example, fillers, binders, disintegrants, lubricants and glidants, and either filling the mixture into 2-piece hard gelatin capsules or compressing the mixture into tablets.

[0017] The invention will be more clearly understood from the following examples.

Example 1

[0018] 500 g of fenofibrate was mixed with 500 g of lactose monohydrate powder, and the mixture was

micronized on an air-jet mill. 2 piece hard gelatin capsules were then filled with the resultant co-micronized powder to a net fill weight of 400 mg per capsule, so that each capsule contained 200 mg of fenofibrate.

Example 2

[0019] 500 g of fenofibrate was mixed with 500 g of microcrystalline cellulose, and the mixture was micronized on an air-jet mill. 2-piece hard gelatin capsules were then filled with the resultant co-micronized powder to a net fill weight of 400 mg per capsule, so that each capsule contained 200 mg of fenofibrate.

Example 3

[0020] For comparison purposes, a quantity of pure fenofibrate was micronized using the same air-jet mill.

[0021] A sample of the pure micronized fenofibrate was then mixed with an equal weight of lactose monohydrate power. 2-piece hard gelatin capsules were then filled with the resultant mixture to a net fill weight of 400 mg per capsule, so that each capsule again contained 200 mg of fenofibrate.

Dissolution Results

[0022] Capsules of examples 1 and 2 were compared to capsules of example 3 for dissolution rate.

[0023] The equipment used for dissolution testing was United States Pharmacopoeia Apparatus #2. The paddle speed was 100 rpm, and the medium was 900 mL of 0.1N sodium dodecyl sulfate water.

[0024] It was found that, in 60 minutes, over 90% was dissolved from the capsules of examples 1 and 2, whereas only 50% to 70% was dissolved for the capsules of example 3.

[0025] It is thus clear that the dissolution rate is substantially higher using fenofibrate that has been co-micronized with a solid excipient such as lactose or microcrystalline cellulose, in comparison to fenofibrate that has been micronized in pure form and then mixed with a solid excipient.

Claims

1. A pharmaceutical composition comprising a co-micronized mixture of fenofibrate and a solid excipient that is not a surfactant.

2. A composition as in claim 1 wherein the mean particle size of the said co-micronized mixture is less than 15 microns.

3. A composition as in claim 1 wherein the mean particle size of the said co-micronized mixture is less than 10 microns.

4. A composition as in claim 1 wherein the mean particle size of the said co-micronized mixture is less than 5 microns.

5. A composition as in any of claims 1 to 4, wherein the ratio of the excipient to fenofibrate by weight is from about 1:100 to about 2:1.

6. A composition as in any of claims 1 to 4, wherein the ratio of the excipient to fenofibrate by weight is about 1:10 to about 3:2.

7. A composition as in any of claims 1 to 4, wherein the ratio of the excipient to fenofibrate by weight is about 1:1.

8. A composition as in any of claims 1 to 5, wherein the excipient is selected from the group consisting of microcrystalline cellulose, lactose, and starch.

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EUROPEAN SEARCH REPORT

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EP 00 30 3077

DOCUMENTS CONSIDERED TO BE RELEVANT

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TECHNICAL FIELDS SEARCHED (Int.Cl.7)

A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	17 October 2000	Scarponi, U

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82